CHAPTER V

DISCUSSION

There were 27 gout patients with renal insufficiency enrolled and complete in this study. Most patients were male and the prevalence of gout could be found in the age ranged from 42 to 72 years old. Hypertension and dyslipidemia were often found in patients with gouty arthritis. The majority of patients could controlled blood pressure within satisfy level. However, duration of gout was not completely normal distributed, this was probable due to very wide range of duration (1month-20 years) while number of samples were too small.

All gout patients in this study were not restricted in purine diet intake because purine-free diet could affect only 1 -1.2 mg/dl decrease in serum urate level. High purine intake was not the main factor which will induce hyperuricemia in gout patients[3], however, acute attacks might be triggered by high purine intake.

In table 8, most patients had their Scr and BUN within normal ranges except for a few cases (patient no. 1, 5 and 26) who had Scr >2.0 mg/dl and BUN > 30 mg/dl at both periods, before and after treatment. None of the patients had condition of oliguria or polyuria at both periods. There were three patients who showed proteinuria which were higher than 1 g/day after treatment (patient no.1, 11and 26), however, high protein had already been existed in their urines since before treatment. Receiving allopurinol 300 mg/day for 6 weeks did not showed any significantly change in any laboratory data that reflect renal function of gout patients with renal insufficiency.

In table 9, data of patients number 26 showed quite high trough and peak oxypurinol concentration (78.18, 88.85 μg/ml, respectively), prolong half life ($T_{1/2}$=

102.9 hr.), and low Vd (18.6 l). Besides, his CrCl at baseline was quite low (28.6 ml/min), BMI was less than 20 kg/m^2 (17.1 kg/m^2). After treatment, CrCl was decreased to 24.5 ml/min, at the same time, serum urate decreased to satisfy level (5.2 mg/dl). Patients with CrCl less than 30 ml/min and malnutrition were sensitive group which require carefully monitoring when using allopurinol in high standard dose for long time. Dosage of allopurinol should initially be less than 300 mg/day while follow up their serum urate, CrCl, sign and symptom of adverse events. After using allopurinol for long term treatment, if serum urate was stable at less than 6 mg/dl or preferably below 5 mg/dl in tophi cases, adjusting to lower dosage is recommended.

Since CrCl of each patient were varied at baseline and figure 3 showed that there were statistically significant relationship between CrCl and clearance of oxypurinol, therefore, administration the patients with equal dosage of allopurinol could result in different in plasma oxypurinol concentration in each patient.

In figure 3, there were significantly linear correlation between CrCl and clearance of oxypurinol. The clearance of oxypurinol could be estimated from CrCl according to the equation:

$$y = 0.1583x - 0.5358 \quad \text{.....equation 1}$$

where ; y was clearance of oxypurinol (ml/min) and x was CrCl (ml/min)

After oxypurinol clearance is estimated from equation 1, maintenance dose which could produce a desired average plasma oxypurinol concentration at steady state could then be calculated with equation 2 :

$$\text{Maintenance dose} = \frac{Cl \times C_{pss\,ave} \times \tau}{S \times F} \quad \text{.....equation 2}$$

where ; Cl = clearance of oxypurinol (l/hr)

$C_{pss\,ave}$ = desired average plasma oxypurinol concentration at steady state (mg/l or μg/ml)

τ = dosing interval

S = fraction of administered salt form (S =1.0)

F = the bioavailability factor (F =0.85)

From the results in table 10 and 11, there were six patients whose CrCl were decreased more than 4 ml/min after treatment (patient no. 1, 5, 14, 16, 21,26). While there were seven patients whose CrCl were increased more than 4 ml/min after treatment, thus, comparison between the mean values before and after allopurinol treatment showed no statistically significant difference. However, there were tendency that the proportions of patient with decrement of CrCl $\geq$ 4 ml/min would increase in patient groups with higher concentrations of either peak or trough oxypurinol levels. However, these increases in proportions among different ranges of plasma concentrations were not significantly for both peak and trough levels which might due to the small number of patients. However, when individual cases was observed, there was one case (patient no. 1) whose CrCl was decreased more than 10 ml/min after treatment (>20% from baseline), and another case (patient no. 14) whose CrCl was 9.14 ml/min lower after treatment (>15% from baseline). Their trough levels were 20.34 and 35.18 µg/ml and peak levels were 27.73 and 48.13 µg/ml, respectively. Obviously, both patients were gout with chronic renal disease. Therefore, the main factor of decreasing CrCl in both cases could be due to the individual progression of renal disease and ability to control this disease, or might actually due to the high levels of plasma peak and trough concentrations in the second case

Table 12, Comparison of mean pharmacokinetic parameters among the three groups (with differences in their changes of CrCl after treatment) indicated that CrCl could be decreased after allopurinol treatment in patients who had the lower values of Kd and/or clearance of oxypurinol, while patients with high values of these parameters were likely to have positive effect on CrCl, i.e., their CrCl were either changed within 4 ml/min or even increasing after allopurinol treatment. Although, there were no

significantly different among the three groups, but group 2 (patients with CrCl decreased $\leq$ 4 ml/min) had most prolong $T_{1/2}$. These results might help confirming that plasma oxypurinol concentration could be associated with decreasing in CrCl after allopurinol treatment.

Because of the small sample size in this study, the differences in the pharmacokinetic parameters among the three groups might need further confirmed with a larger sample size trial.

The results in table 14 indicated that using allopurinol 300 mg/day for 6 weeks was able to control serum urate level to decrease to optimal range, for approximately 70 percents of the patients with no tophi. However, only one patient with tophi (10%) met the treatment goal, indicated that patients with renal insufficiency and tophi required higher than 300 mg/day doses of allopurinol. Table 22, 23 and figure 12, 13 showed that there were significantly linear correlation between trough or peak levels and the changes in serum urate levels. Therefore, change in serum urate level was depended on plasma oxypurinol concentration. From the results of this study, almost all patients with renal insufficiency had their plasma oxypurinol concentrations which were higher than the therapeutic range, which was recommended for patients with normal renal function. Since both uric acid and oxypurinol were mainly excreted by kidney route, excretion of both substances in patients with renal insufficiency, were diminished. Although, in this type of patients, oxypurinol levels had already highly accumulated in plasma, but there were still not high enough to decrease the high serum urate levels down to target level (table 20, 21). Therefore, the therapeutic range of normal renal function should not be used as reference for patients with renal insufficiency.

There were nine patients with tophi whose serum urate level did not meet $\geq$ 5 mg/dl goal. Most patients had trough and peak levels in the ranged of 15-25 μg/ml and 25-30 μg/ml, respectively. The failure of controlling serum urate to reach the target level was possibly related to the low levels of plasma oxypurinol concentration. Therefore,

patients with tophi might higher plasma oxypurinol concentration levels of higher than 35 μg/ml for trough and higher than 45 μg/ml for peak, in order to effectively dissolution of urate deposit. In addition, the five patients without tophi (25%) whose serum urate level could not achieve the target level had their trough plasma levels in the ranged of 7-20 μg/ml while their peak levels were in the ranged of 15-30 μg/ml. These patients might require higher doses in order to reach higher plasma levels and in turn, their serum urate level could decrease to the target goal. Thus, for patients without evidence of tophi, the proposed plasma oxypurinol concentrations might be higher than 25 μg/ml for trough level, and higher than 35 μg/ml for peak level.

Table 17 and 18 showed that there was one patient whose trough level was ≥35 μg/ml and peak level was ≥45 μg/ml, but his serum urate still could not met the therapeutic goal, i.e., his serum urate after treatment still higher 6.0 mg/dl (7.8mg/dl). Detail observation revealed that his serum urate could not achieve to target level because his serum urate was very high from the beginning (14.5 mg/dl), and he also presented evidence of tophi, his serum urate was required to change more than 8.5 mg/dl for target level of 6.0 mg/dl, or more than 9.5 mg/dl for target level of below 5 mg/dl. This patients should be monitored for his serum urate for a longer period of time, if the higher level of serum urate still exist, it might imply that oxypurinol levels of this case (trough;32.14μg/ml, peak;43.13μg/ml) were still not high enough for controlling his serum urate. Thus, his allopurinol dosage might need to be adjusted to higher than 300 mg/day with carefully monitoring.

Table 19 and 20 showed that there were tendency of increasing in proportion of patients with decreased urate excretion of more than 200 mg/ 24 hr when trough and/or peak level were in the higher ranges, but these increment were not consistent at the highest level since those three patients with trough level ≥35 μg/ml and/or with peak μg/ml ≥45 μg/ml whose urate excretion could not decrease ≥ 200 mg/24hr had their urate

excretion at baseline which were less than 300 mg/24 hr. Therefore, it was impossible for these patients to have their urate excretion more than 200 mg/24hr.

Allopurinol is the inhibitor of xanthine oxidase, which is the enzyme required for production of uric acid. This drug does not have any mechanism involve kidney which could affect urate excretion, thus decreasing in excretion of urate could be influenced from efficacy of allopurinol treatment in reducing serum urate production.